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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/247,886	02/10/99	PUNNONEN J	18097-030200

020350 HM22/1013
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EXAMINER	
CHEN,S	
ART UNIT	**PAPER NUMBER**
1633	9

DATE MAILED: 10/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/247,886	Punnonen et al.
Examiner	**Group Art Unit**
Shin-Lin Chen	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-58 is/are pending in the applicat

Of the above, claim(s) 24-58 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5, 6

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

The preliminary amendment filed 9-5-00 has been entered. Claims 18 and 24 have been amended. Claims 51-58 have been added.

1. Claims 24-50 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 4.

2. Applicant's election with traverse of group I, claims 1-23, in Paper No. 8 is acknowledged. The traversal is on the ground(s) that claim 22 recites expressing a fusion protein on the surface of a replicable genetic package, and claims 24-20 and 33-35 do not recite anything about a replicable genetic package. This is not found persuasive because claim 22 only recites a genetic vaccine vector but does not specify expressing a fusion protein on the surface of a replicable genetic package, and claims 24-30 and 33-35 are drawn to a method to identify the APCs containing a vector comprising a at least **any** two forms of a polynucleotide or a replicable genetic package such as phage specifically binds to APCs which is different from the method drawn by group I. Thus, groups I and II are drawn to different methods for different purposes.

The requirement is still deemed proper and is therefore made FINAL.

Claims 51-58 are drawn to a method for obtaining an optimized recombinant cell-specific binding moiety **polypeptide** useful for increasing uptake, efficacy, or specificity of a vaccine antigen by a target cell. Thus, claims 51-58 are drawn to a noneleted invention and are

withdrawn from consideration by the examiner. Claims 1-58 are pending and claims 1-23 are being considered.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "the polynucleotide that encodes a nucleic acid binding domain and/or a further form of the polynucleotide that encodes a cell-specific ligand" in claim 3 is vague and renders the claim indefinite. It is unclear what is intended by the claimed invention, a polynucleotide that encodes a nucleic acid binding domain or a polynucleotide that encodes a cell-specific ligand, or both?

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods disclosed by Ledley et al., 1994 (AH), Patten et al., 1997 (BG) and Stemmer et al. 1997 (AG), wherein said methods comprising recombining at least first and second forms of a nucleic acid encoding a nucleic acid binding domain and a cell-specific ligand that specifically binds to the surface of the target cell to create a library of recombinant binding moiety-encoding nucleic acids by iterative selection and recombination and to screen the optimized recombinant cell-specific binding moiety nucleic acids, does not reasonably provide enablement for a method for obtaining a cell-specific binding molecule useful for increasing uptake or specificity of a genetic vaccine to a target cell by recombining at least first and second forms of a nucleic acid encoding a nucleic acid binding domain and a cell-specific ligand to create a library of recombinant binding moiety-encoding nucleic acids by any method other than the iterative selection and recombination as discussed above and to screen the optimized recombinant cell-specific binding moiety nucleic acids, and any genetic vaccine comprising said cell-specific recombinant binding moiety. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-13 and 18-23 are directed to a method for obtaining a cell-specific binding molecule useful for increasing uptake or specificity of a genetic vaccine to a target cell by recombining at least first and second forms of a nucleic acid encoding a nucleic acid binding

domain and a cell-specific ligand that specifically binds to the surface of the target cell to create a library of recombinant binding moiety-encoding nucleic acids and to screen the optimized recombinant cell-specific binding moiety nucleic acids. Claims 18-23 specify the use of a polynucleotide encoding a non-toxic receptor binding moiety of an enterotoxin. Claim 14-17 are directed to a cell specific recombinant binding moiety produced by the method set forth above and a genetic vaccine comprising said cell-specific recombinant binding moiety.

The specification of the present application fails to provide an enabling disclosure for a method of recombining at least first and second forms of a nucleic acid encoding a nucleic acid binding domain and a cell-specific ligand that specifically binds to the surface of the target cell to obtain a cell-specific binding moiety useful for increasing uptake or specificity of a genetic vaccine by any method other than the iterative selection and recombination as discussed above, or for a genetic vaccine comprising said cell-specific binding moiety.

The specification indicates the use of error-prone PCR or cassette mutagenesis for recombining the nucleic acids. Stemmer et al., 1998 (AE) points out that the error-prone PCR suffer from a low processivity of the polymerase, and is unable to result in the random mutagenesis of an average-sized gene and limits the practical application of error-prone PCR. Stemmer also reports that in error-prone PCR "the rate of down-mutations grow with the information content of the sequence. At a certain information content, library size, and mutagenesis rate, the balance of down-mutations to up-mutations will statistically prevent the selection of further improvements (statistical ceiling). Finally, repeated cycles of error-prone

PCR will also lead to the accumulation of neutral mutations, which can affect, for example, immunogenicity but not binding affinity". Further, "In cassette mutagenesis, a sequence block of a single template is typically replaced by a (partially) randomized sequence. Therefore, the maximum information content that can be obtained is statistically limited by the number of random sequences (i.e. library size). This constitute a statistical bottleneck, eliminating other sequence families which are not currently best, but which may have greater long term potential" (e.g. column 2). In addition, the specification also fails to provide enabling disclosure for any genetic vaccine containing the cell-specific binding moiety produced by the claimed invention which stimulates immune response in a host and shows protection of said host from a particular disease or disorder.

In view of the problems set forth above for the error-prone PCR and cassette mutagenesis, it is unclear whether the claimed invention could provide a cell-specific binding moiety having increased uptake or specificity of a genetic vaccine for a target cell. It is also unclear whether the claimed invention could provide any genetic vaccine containing said cell-specific binding moiety which stimulate the desired immune response for the protection of a host against a specific disease or disorder. It is unpredictable whether one of skilled in the art at the time of the invention would be able to provide a cell-specific binding moiety having increased uptake or specificity of a genetic vaccine for a target cell, and any genetic vaccine containing said cell-specific binding moiety which stimulate the desired immune response for the protection of a host against a specific disease or disorder. Thus, one skilled in the art at the time of the invention

would require undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the lack of working examples, and the breadth of the claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. 1997 (AG) in view of Ledley et al., 1994 (AH) and Patten et al., 1997 (BG).

Claims 1-13 and 18-23 are directed to a method for obtaining a cell-specific binding molecule useful for increasing uptake or specificity of a genetic vaccine to a target cell by

recombining at least first and second forms of a nucleic acid encoding a nucleic acid binding domain and a cell-specific ligand that specifically binds to the surface of the target cell to create a library of recombinant binding moiety-encoding nucleic acids and to screen the optimized recombinant cell-specific binding moiety nucleic acids. Claims 18-23 specify the use of a polynucleotide encoding a non-toxic receptor binding moiety of an enterotoxin. Claim 14-17 are directed to a cell specific recombinant binding moiety produced by the method set forth above and a genetic vaccine comprising said cell-specific recombinant binding moiety.

Stemmer teaches a method for the production of nucleic acid fragments or polynucleotides encoding mutant proteins by repeated cycles of mutagenesis, shuffling and selection of nucleic acids to generate polynucleotides having desired characteristic by iterative selection and recombination for the molecular evolution *in vitro* or *in vivo* of proteins (e.g. abstract). Stemmer teaches a method of evolving a polynucleotide sequence toward a desired property comprising recombining at least a first and second forms of the polynucleotide sequence to produce a library of recombinant forms of the sequence, screening at least a first recombinant sequence from said library, recombining said first recombinant sequence with a further form of the polynucleotide sequence, the same or different from the first and second forms, to produce a further library, and screening at least one further recombinant polynucleotide from said further library (e.g. p.164).

Stemmer does not teach generating a chimeric recombinant DNA comprising a DNA binding domain and a ligand which binds to the surface of a target cell, and does not teach using DNA shuffling or recombination to generate a genetic vaccine with a desired properties.

Ledley teaches generating a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA, such as histone or transacting regulatory element, and a complex for gene transfer comprising a DNA molecule specifically and non-specifically bound to the chimeric recombinant DNA-binding protein (e.g. p. 26, 27, abstract).

Patten teaches "viral vaccine vectors can be enhanced by DNA shuffling to give desired properties of tropism, stability and expression level", and DNA shuffling could be a tool " for increasing the efficiency and success rate of the development of novel whole organism, viral, bacterial and recombinant protein vaccines" (e.g. p. 732).

It would have been obvious for one of ordinary skill in the art at the time of the invention to substitute the first and second forms of polynucleotide sequences taught by Stemmer with polynucleotide sequences encoding a DNA-binding element and a ligand binding to a receptor on a target cell as taught by Ledley for the production of a genetic vaccine as taught by Patten.

One having ordinary skill at the time of the invention would have been motivated to do so because the generation of a chimeric recombinant DNA-binding protein comprising a first element for binding to a receptor on a target cell and a second element required for binding to DNA could facilitate the efficiency of gene transfer and the effects of a genetic vaccine

comprising a polynucleotide sequences containing a nucleic acid binding site and an optimized recombinant binding moiety containing a nucleic acid binding domain and a cell-specific ligand.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J.R. CLARK
PRIMARY EXAMINER

Shin-Lin Chen, Ph.D.